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Cerebellar Mutism Syndrome and Other Complications After Surgery in the Posterior Fossa in Adults: A Prospective Study

Morten Wibroe^{1,2}, Per Roehat¹, Marianne Juhler¹

■ BACKGROUND: Cerebellar mutism syndrome (CMS) is rarely described in adults; however, data on self-assessed linguistic complications after posterior fossa surgery do not exist.

■ METHODS: Through a prospective single-center study, data on 59 tumor operations in the posterior fossa were collected preoperatively as well as 1 week and 1 month postoperatively. Data on self-assessed problems in 5 CMS-related domains, CMS scores, and neurology as well as surgical procedure and complications were obtained.

■ RESULTS: Data on CMS-related complications were obtained on 56 of the 59 operations. None was found to have CMS according to the CMS score. Within each of the 5 domains, at least 9 operations (16%) were followed by development or worsening of self-assessed CMS-related complications. Self-assessed complications were found to be most frequent after primary tumor surgeries, although they were significant only for speech and motor complications (P value = 0.01 and 0.02). Speech and language complications occurred more frequently in midline tumors compared with lateral tumors (40% vs. 7%; P = 0.004). Surgical complications were similar to other studies.

■ CONCLUSIONS: We propose that speech and language problems in adults undergoing surgery in the posterior fossa occur more frequently than previously assumed. Some of the self-assessed complications might reflect components of the cerebellar cognitive affective syndrome.

Our findings are consistent with the fact that midline location of the tumor is one of the few known risk factors for CMS in children. Thus, the cerebellar midline seems to be a vulnerable region for speech and language complications also in adults.

INTRODUCTION

Cerebellar mutism syndrome (CMS) is a well-known complication of surgery in the posterior fossa in children and adolescents. CMS refers to the constellation of transient mutism and emotional lability frequently accompanied by other motor, cognitive, and cranial nerve impairments.¹ The reported incidence of CMS after this type of surgery in children and adolescents ranges from 8% to 39%²⁻⁶ depending on the definitions and inclusions. In adults, CMS has been described only in sporadic case reports. In 2013, Mariën et al.⁷ found that only 21 cases of postoperative CMS in patients older than 18 years had ever been reported in the literature. Since then, 1 additional case of adult CMS has been reported.⁸ Thus, CMS seems to be an extremely rare complication in adults. However, no earlier studies have systematically and prospectively investigated the incidence of CMS or other postoperative speech and language complications after posterior fossa surgery in adults.

Compared with the extensive literature on complications to surgery in the supratentorial space, reports on complications after surgery in the posterior fossa are sparse. Some studies have

Key words

- Adults
- Brain tumor
- Cancer
- Cerebellar cognitive affective syndrome
- Cerebellar mutism syndrome
- CMS
- Neurosurgery

Abbreviations and Acronyms

CCAS: Cerebellar cognitive affective syndrome

CMS: Cerebellar mutism syndrome

CSF: Cerebrospinal fluid

DTCT: Dentatohalamic-cortical

SMA: Supplementary motor area

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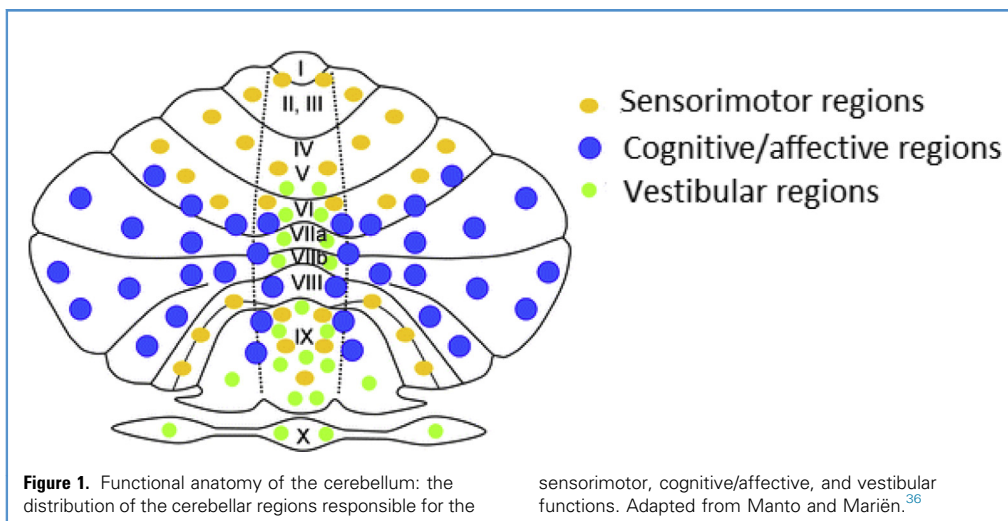
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investigated the complications of general intra-axial brain tumor surgery including both supratentorial and infratentorial tumors⁹⁻¹¹ but few have focused solely on posterior fossa surgery.¹²⁻¹⁴ Of the latter, the most comprehensive and the only one to find post-operative speech and language problems is a systematic retrospective investigation of 500 patients in a mixed population of children and adults.¹⁴ This study found that the overall rate of complications was 31.8%, the most common being cerebrospinal fluid (CSF) leakage (13%), meningitis (9.2%), and wound infections (7%). Reported neurologic complications were cranial nerve palsies in 4.8% and CMS in 6 patients (1.2%). Other neurologic complications including other forms of speech and language disturbances were not investigated. It is not possible to distinguish between complications in adults and children in this study. Furthermore, because most of the study group (83%) had extracerebellar surgeries and only 17% of the cases were intracerebellar, the risk of CMS or CMS-like conditions after lesionectomy in the cerebellum is probably underestimated in this study. Additional complications reported by other studies include pseudomeningocele, rhinorrhea, and cerebellar infarcts.^{12,13}

Oropharyngeal dyspraxia and swallowing problems are categorized as part of CMS, and in this context, it is interesting that another retrospective survey reported 56 cases of dysphagia after posterior fossa surgery in adults over a 3-year period. The risk percentage was not calculated and additional speech or language problems were unreported.¹⁵

The pathophysiology behind CMS remains unknown although multiple theories have been proposed.¹⁶ It is equally unclear why the risk of CMS should be higher in children than in adults.

It is now recognized that the cerebellum is not exclusively a motor control organ but also has cognitive, emotional, and behavioral functions (Figure 1).^{17,18} There is increasing evidence that CMS is associated with bilateral disturbance of the dentate nuclei^{5,19-23} and their efferent cerebellothalamic-cerebral connections (Figure 2).^{16-18,24,25} Some of the symptoms may thus be results of secondary diaschisis in supratentorial brain areas.²⁶⁻²⁸

Other proposed injury mechanisms include cerebellar perfusion deficits caused by vasospasm, axonal perioperative injury, post-operative edema, alterations in neurotransmitter levels, synaptic

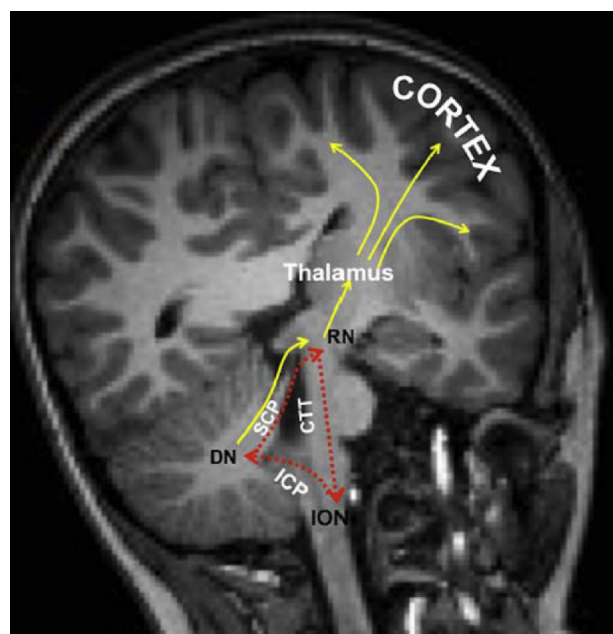


Figure 2. Neural pathways related to cerebellar mutism syndrome (CMS). The cerebral cortex and cerebellum are in circuit via several different projections. The most important of these projections regarding CMS is the dentatothalamic-cortical tract (DTCT) traveling via the dentate nucleus (DN) along the superior cerebellar peduncle (SCP) to the contralateral cerebral cortex via the contralateral red nucleus (RN) and thalamus. Another pathway of possible importance is the Guillain and Mollaret triangle formed by efferent tracts ascending from the DN via the superior cerebellar peduncle to the contralateral red nucleus, descending via the central tegmental tract (CTT) to the inferior olivary nucleus (ION) and back to the contralateral DN via the inferior cerebellar peduncle (ICP). Adapted from Avula et al.¹⁶

Table 1. Basic Patient and Tumor Data

	n	%
Mean age, years (standard deviation)	51.2 (16.8)	
Female	33	56
Reoperations	7	12
Cause		
Carcinoma metastasis	34	57
Hemangioblastoma	8	14
Glioblastoma	4	7
Pilocytic astrocytoma	4	7
Medulloblastoma	3	5
Ependymoma	2	3
Subependymoma	2	3
Epidermoid	1	2
Lymphoma	1	2

or transsynaptic degeneration, and thermal injury related to the use of ultrasonic aspirators.¹⁶ None of these factors seems to explain a difference in CMS risk between adults and children. It has been hypothesized that uncompleted myelination could explain why the pathways in children could be more vulnerable.²⁹ Medulloblastoma histology, midline location, and brainstem tumor involvement are known risk factors for CMS in children. The biological mechanisms behind these associations are uncertain.^{2,19,30-34}

There are no studies systematically documenting the risk of CMS or similar neurologic dysfunction in adults. The risk could be underreported, and the aim of this study is therefore consecutively and prospectively to investigate the occurrence of signs of CMS in adults after posterior fossa surgery. The hallmark of CMS is speech and language dysfunction, which consequently is the main focus of the study. In addition, we register the frequency and type of other complications experienced by these patients.

METHODS

Patients

This project is an observational single-center study. A total of 59 surgeries on 52 adults older than 18 years were included in the study. The patients were consecutively enrolled in the study having given informed consent after admission to the neurosurgical department of University Hospital Rigshospitalet, Copenhagen for tumor surgery or open biopsy in the posterior fossa from October 2013 to March 2015. Patients who had previously received surgery, chemotherapy, and/or radiotherapy were also eligible. Surgery and supportive care were provided according to local practice with additional neurologic examinations for the study.

Slightly more than half of the study population were female. The mean age of the patients was 51.2 years at the time of the surgery (Table 1). Most of the tumors were carcinoma metastasis including metastasis of adenocarcinomas, small-cell and non-small-cell carcinomas, urothelial carcinomas, planocellular carcinomas, and neuroendocrine carcinomas. Hemangioblastoma was the most common primary tumor (Table 1).

Neurologic Assessment

Neurologic function was registered before surgery and post-operatively within 1 week. The patients rated 5 different cerebellar functions and signs of CMS on a scale from 0 to 10, 0 being "no problems" and 10 being "extreme difficulty." The questions self-assessed in this way were 1) vision (e.g., diplopia, blurry vision, loss of vision), 2) motor skills (e.g., ataxia, hypotonia, loss of balance), 3) speech (dysarthria), 4) language (word finding difficulties), and 5) other cognitive functions (impaired memory, attention and/or comprehension). Neurologic examination including the Brief Ataxia Rating Scale and a Mini-Mental State Examination was also performed. All neurologic assessments were performed by a physician, who did not perform or participate in the surgical procedures.

A previously published standardized surgical form for evaluating posterior fossa surgery was completed within 72 hours after the operation by the operating neurosurgeon. The form contains information on tumor location, surgical route (Figure 3), duration

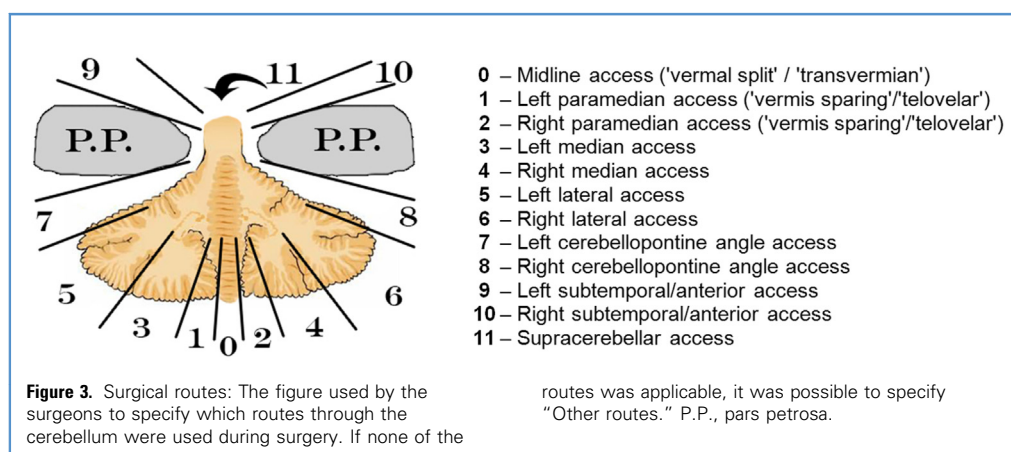


Table 2. Tumor Location and Surgical Route

	n	Percentage of Operations
Tumor Location		
Cerebellar vermis	2	4
Right cerebellar hemisphere	26	46
Left cerebellar hemisphere	15	27
Fourth ventricle	15	27
Brainstem	3	5
Surgical route		
0, Midline	8	14
1, Left paramedian	6	11
2, Right paramedian	9	16
3, Left median	5	9
4, Right median	12	21
5, Left lateral	7	13
6, Right lateral	8	13
7, Left cerebellopontine angle	0	0
8, Right cerebellopontine angle	2	4
9, Left subtemporal	0	0
10, Right subtemporal	0	0
11, Supracerebellar	2	4
Other*	5	9

The percentages indicate the proportion of operations related to different locations respectively surgical routes and thus add to more than 100%.

*Includes infracerebellar and retrosigmoid access routes.

of surgery, bleeding and vascular injury, technology used, and extent of tumor resection.³⁵

Postoperatively, self-assessment and neurologic examination were repeated as soon as possible within the first week after the operation. In addition, signs of CMS were assessed by the criteria and scoring system published by Robertson et al.²: occurrence of

muteness, reduced speech, ataxia, hypotonia, and irritability/emotional lability.

Signs of CMS were assessed again 1 month after surgery and if present were scored according to Robertson's scoring system as "mild" if the duration was less than 1 week, "moderate" if it lasted from 1 to 4 weeks and "severe" if it persisted for more than 4 weeks.² At this time, information on surgical postoperative complications was also collected systematically by clinical interview and/or review of the medical record. Complications registered were CSF leakage, meningitis, wound infections, hydrocephalus, intracranial hematoma, and death according to the most frequent complications reported in a study on 500 posterior fossa surgeries.¹⁴ Other medical conditions not directly related to the central nervous system were not included (e.g., pneumonia, urinary tract infections, sepsis, deep vein thrombosis, and pulmonary embolism).

Patients undergoing reoperation during the 17-month study period restarted the follow-up program from that date. A new preoperative and all the postoperative registrations were performed again.

All P values were calculated using a 2-sided χ^2 test or Fisher exact test if the expected numbers were less than 5. A P value <0.05 was defined as significant.

The regional ethics committee for the Capital region in Denmark was informed about this study but ethical approval was not necessary because of the observational character of the study.

RESULTS

Tumor Locations and Surgical Routes

Of the 59 surgeries included, 3 were excluded from the analyses: 2 patients died and 1 had a tracheal cannula precluding the chosen assessment of CMS complications. We thus report outcomes for the remaining 56 surgeries.

Tumor locations are shown in Table 2. Some tumors involved more than 1 location and were operated on by more than 1 surgical route. The percentages indicate in how many of the 56 surgeries different locations and surgical routes were involved and thus add to more than 100%. Hemispheric involvement was seen in 73% of the cases, whereas midline structures (cerebellar vermis, fourth ventricle, and brainstem) were involved less frequently.

Table 3. Self-Assessed Complications and Mean Scores

Self-Assessed Complication	Worsening, n (%)	Worsening, Mean Score	Improvement, n (%)	Improvement Mean Score	No Change, n (%)
Vision	9 (16)	−4	10 (16)	3	37 (66)
Motor skills	13 (23)	−4	28 (50)	3	17 (30)
Speech	10 (18)	−3	9 (16)	3	37 (66)
Language	10 (18)	−2	9 (16)	2	37 (66)
Other cognitive functions*	10 (18)	−3	7 (13)	2	39 (70)

*Includes impaired memory, attention, and/or comprehension.

Table 4. Postoperative Cerebellar Mutism Syndrome Complications

Cerebellar Mutism Syndrome Symptom	Not Seen	Mild (<1 week)	Moderate (1–4 weeks)	Severe (>4 weeks)
Mutism	56	0	0	0
Reduced speech	56	0	0	0
Ataxia	50 (42)*	1	2	3
Hypotonia	56	0	0	0
Irritability	56	0	0	0

*Postoperative ataxia was found in 14 cases. Eight of these had preoperative ataxia. Six had exclusively postoperative ataxia.

Accordingly, the most used surgical access routes were access through the right cerebellar hemisphere (right paramedian, median, and lateral routes accounted collectively for 29 [52%] of the operations). The vermis was split though a midline access in 8 (14%) of the operations. In 5 operations (9%), other access routes were used, including infracerebellar and retrosigmoid routes.

Neurologic Outcome

Table 3 shows the outcome in the 5 self-assessed domains. Within each domain, self-reported symptoms were either unchanged or improved in approximately 80% of the operations. Unchanged symptoms also included absence of symptoms in a particular domain at any time. Some patients reported worsening or improvement in more than 1 domain. Only 1 patient (2%) reported worsening in all 5 domains.

By neurologic examination, postoperative ataxia was found in 14 cases (25%) and was the only objective finding within the CMS

spectrum seen in any of the patients, because none of the patients was found to have postoperative mutism, reduced speech, hypotonia, or irritability (**Table 4**). Of the 14 cases found with postoperative ataxia, 8 cases (14% for the total cohort) had preoperative ataxia, and 6 patients (11% of the total cohort) developed postoperative ataxia, which was scored as “severe” (3 patients), “moderate” (2 patients), and “mild” (1 patient).

The associations between the self-assessed complications, tumor type, tumor location, and surgical route are shown in **Tables 5–7**. Self-assessed complications were found to be more frequent after primary tumor surgeries than after metastatic surgeries even although the differences were only significant for motor and speech complications and borderline significant for language complications.

All complications except vision impairment were significantly more frequent in cases with midline tumors compared with cases with lateral tumors, as shown in **Table 6**. The differences were greatest regarding speech and language ($P = 0.004$, Fisher exact test).

All complications were evenly divided among the different types of surgical routes (**Table 7**, see **Figure 2** for reference on surgical routes). However, when the access routes are dichotomized into either midline related or lateral, postoperative speech and language problems tend to occur more frequently in surgeries in or close to the cerebellar midline. However, the differences are not significant ($P = 0.9$, Fisher exact test). Speech or language problems were reported in 7/18 (39%) of operations involving a left-sided approach versus 2/31 (6%) of any right-sided approach ($P = 0.008$, Fisher exact test).

Other Surgical Complications

Of the original 59 operations included, 29 operations (49%) were associated with 1 or more surgical complications (**Table 8**). The most frequent were leakage of CSF (14%), hydrocephalus (14%), and infections (10%).

Table 5. Worsening According to Tumor Type

Tumor Type	Vision	Motor	Speech	Language	Other Cognitive Functions*
Carcinoma metastasis (n = 32), n (%)	4 (13)	4 (13)	2 (6)	3 (9)	5 (16)
Primary tumors (n = 24), n (%)	5 (21)	9 (38)	8 (33)	7 (29)	5 (21)
Hemangioblastoma (n = 8)	0	1	0	0	1
Pilocytic astrocytoma (n = 4)	1	2	1	2	0
Glioblastoma (n = 3)	2	3	3	2	0
Medulloblastoma (n = 3)	0	0	2	1	1
Ependymoma (n = 2)	0	2	0	0	1
Subependymoma (n = 2)	1	1	1	1	1
Epidermoid (n = 1)	1	0	1	1	1
Lymphoma (n = 1)	0	0	0	0	0
P values†	0.48	0.03	0.01	0.08	0.7

*Includes impaired memory, attention, and/or comprehension.

†P values are calculated using χ^2 tests or Fisher exact test comparing metastasis surgeries with primary tumor surgeries.

Table 6. Worsening According to Tumor Location

Tumor Location	Vision	Motor	Speech	Language	Other Cognitive Functions*
Midline locations (n = 20), n (%)	5 (25)	8 (40)	8 (40)	8 (40)	5 (25)
Cerebellar vermis (n = 2)	0	1	1	2	1
Fourth ventricle (n = 15)	4	6	7	6	4
Brainstem (n = 3)	1	1	0	0	0
Lateral locations (n = 41), n (%)	4 (10)	5 (12)	3 (7)	3 (7)	5 (12)
Right cerebellar hemisphere (n = 26)	3	2	1	1	2
Left cerebellar hemisphere (n = 15)	1	3	2	2	3

Some tumors were registered in more than 1 location.

*Includes impaired memory, attention, and/or comprehension.

DISCUSSION

This study is the first of its kind to prospectively test for objective and subjective signs of CMS after posterior fossa surgery in an adult population. In 1998, Schmähmann and Sherman identified “The cerebellar cognitive affective syndrome” (CCAS or Schmähmann syndrome).^{17,36} This syndrome is characterized by impairment of executive deficits, difficulties with spatial cognition, personality change, and language deficits and some investigators have suggested a link between CCAS and CMS in children.^{37,38} The syndrome was first identified in a group of 20 adult patients with etiologically different cerebellar disorders. Based on this finding, it would be expected to find such disturbances after posterior fossa surgery in adult patients.

Our aim was to investigate if adult patients operated on in the posterior fossa show or experience any signs of CMS, and we therefore added a self-assessment score for 5 domains related to CMS in addition to the Robertson criteria, which have long been accepted and used for children.² We found that in each of the 5 domains, the patients reported new development or worsening after at least 9/56 corresponding to 16% of the operations. In comparison, none of the patients fulfilled the Robertson criteria for CMS. We propose that the self-assessment is more sensitive and that speech and language problems do occur in adults undergoing surgery in the posterior fossa more frequently than previously assumed.^{12–14} Although CCAS is defined by standardized objective tests, it is possible that some of the self-assessed complications in our study may reflect components of CCAS.

Table 7. Worsening According to Surgical Route

Surgical Route	Vision	Motor	Speech	Language	Other Cognitive Functions*
0, Midline (n = 8)	1	2	3	3	1
1, Left paramedian (n = 6)	1	2	1	1	2
2, Right paramedian (n = 9)	1	2	0	0	1
3, Left median (n = 5)	0	1	1	1	1
4, Right median (n = 12)	1	1	1	0	1
All midline related (n = 40), n (%)	4 (10)	8 (20)	6 (15)	5 (13)	6 (15)
5, Left lateral (n = 7)	2	3	1	2	2
6, Right lateral (n = 8)	0	0	0	0	2
7, Left cerebellopontine angle (n = 0)	0	0	0	0	0
8, Right cerebellopontine angle (n = 2)	1	1	1	0	0
9, Left subtemporal (n = 0)	0	0	0	0	0
10, Right subtemporal (n = 0)	0	0	0	0	0
All lateral (n = 17), n (%)	3 (18)	4 (24)	2 (12)	2 (12)	4 (24)
11, Supracerebellar (n = 2)	0	1	0	1	0
12, Other (n = 5)	2	1	2	2	1

Some tumors were operated on using more than 1 route.

*Includes impaired memory, attention, and/or comprehension.

Table 8. Surgical Complications

	n	%
Cerebrospinal fluid leakage	8	14
Hydrocephalus	8	14
Infections	6	10
Hematoma	5	8
Death	2	3

We found that tumors located in or close to midline structures were associated with higher frequencies of self-reported signs of CMS compared with lateral localized tumors. The differences were greatest regarding the self-assessed complications of speech and language function (40% vs. 7%; $P = 0.004$). Similarly, we found that surgical approaches in or close to the midline seemed to carry a higher, although nonsignificant, risk than did lateral approaches for self-assessed speech and language complications (13%–15% vs. 12%). Our findings are consistent with the fact that midline location of the tumor is one of the few known risk factors for CMS in children.³⁹ Thus, the cerebellar midline seems to be a vulnerable region for speech and language complications also in adults, albeit with less severe deficits than in children.

In nonmidline approaches, speech and language problems almost exclusively occurred after surgery from the left rather than the right side (39% vs. 6%; $P = 0.008$). Clinical and imaging studies have indicated that language is heavily right lateralized in the cerebellum.²⁴ Furthermore, other studies have identified a crossed laterality of cerebral and cerebellar language dominance, making the right cerebellar hemisphere dominant for language in people with a left cerebral hemisphere dominance for language.⁴⁰ That the left cerebral hemisphere is dominant for language in 97% of the right-handed population⁴¹ and up to 90% of the background population is right handed⁴² make us expect that speech and language problems are associated with surgery in the right cerebellar hemisphere, contrary to what we found. We did not collect data on the handedness of the patients and thus do not know the exact distribution of hemisphere dominance in our cohort.

The risk for problems in all 5 self-assessed domains was higher in primary tumor surgeries (21%–38%) than in metastatic surgeries (6%–16%). In particular, the risks for self-assessed speech,

motor, and to a lesser degree language complications were found to be more frequent in primary tumor surgeries ($P = 0.01$, 0.02 , and 0.08 , respectively). Our study design does not allow an explanation for this finding. It is likely that the infiltrating nature of many primary tumor types results in more surgical damage to cerebellar tracts.

A probable key substrate in the development of pediatric CMS is the dentatohalamic-cortical (DTCT). Although a recent tractography study found that the DTCT connects the cerebellum with different associative areas,⁴³ 1 study suggests that the DTCT specifically connects cerebellum with the supplementary motor area (SMA).⁴⁴ Lesions in adults involving the SMA can result in a clinical condition known as SMA syndrome.^{45–47} This syndrome shares several features with CMS, including delayed transient mutism and reduced movement. The fact that 2 such separate areas can result in similar clinical presentations speaks in favor of the diaschisis theory behind pediatric CMS described earlier. Furthermore, it indicates that adults might be at risk of symptoms similar to CMS although the anatomic origins might differ. A study from 2010 using whole-head magnetoencephalography found that adults are less likely than children to recruit the SMA and cerebellum during simple tasks.^{48,49} This finding suggests that adults might be less dependent on DTCT in performing certain tasks, which explains why damage to the DTCT in adults does not cause the same diaschisis-induced symptoms of CMS as seen in children. Thus, damage to the SMA might be the root of both CMS and SMA syndrome: In CMS the damage is caused by diaschisis and in SMA syndrome the damage is caused by direct lesions of the SMA. This situation explains the low incidence of CMS after posterior fossa surgery in adults and needs to be further investigated.

Surgical complications in our study are similar in type and number to other studies,^{12–14} with CSF leakage and related complication being the most prominent. However, we did find a higher overall risk of complications (49% vs. 16%–32%) mostly because of an increased risk of hydrocephalus (14% vs. 1%–5%) and leakage of CSF (14% vs. 2.5%–13%).

CONCLUSIONS

Although larger future studies are needed for a better understanding of the association between self-assessed speech and language complications and surgical risk factors, our reported observations can already be useful for surgical planning and for preoperative information for patients on surgical risks.

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